REMARKS

The Pending Claims

Claims 1, 2, 5, 8, 18 and 20-21 are pending and under active consideration. The pending claims are directed to plasmids comprising tightly regulated promoters operatively linked to an isolated and purified PAL DNA sequences.

The Office Action

Claims 1, 2, 5, 8, 18, 20 and 21 are rejected.

Claims 1, 2, 5, 8, 18 and 21 are rejected under 35 U.S.C. § 103(a), as allegedly being unpatentable over Anilionis et al. (WO 90/02557) in view of Nelson et al. (Infection and Immunity, 56(1):128-134, 1988), Guzman et al. (Journal of Bacteriology, 177(14):4121-4130, 1995) and Makrides et al. (Microbiology Reviews, 60(3):512-538, Sept. 1996).

Claims 18 and 21 are rejected under 35 U.S.C. § 103(a), as allegedly being unpatentable over Anilionis et al. (WO 90/02557) in view of Nelson et al. (Infection and Immunity, 56(1):128-134, 1988), Mertens et al. (Gene, 164:9-15, 1995) and Makrides et al. (Microbiology Reviews, 60(3):512-538, Sept. 1996).

Claim 20 is rejected under 35 U.S.C. § 103(a), as being unpatentable over Anilionis et al. (WO 90/02557) in view of Nelson et al. (Infection and Immunity, 56(1):128-134, 1988), Mertens et al. (Gene, 164:9-15, 1995) and Makrides et al. (Microbiology Reviews, 60(3):512-538, Sept. 1996), and further in view of Novagen Inc. allegedly admitted prior art (Specification page 15, line 34).

Amendments

Claim 18 is currently amended. Claims 3, 4, 6, 7, 9-17, 19 and 22 are canceled. The amendments to the claims do not introduce new matter; and are supported by the specification, as originally filed. Particular support for the amendment is found on page 5, fourth paragraph, Example 1 and Figure 1.

Amendment of the claims is made without prejudice and without intent to abandon any originally claimed subject matter. Entry of the amendments is respectfully requested.

Rejection Under 35 U.S.C. § 103(a)

I. Claims 1, 2, 5, 8, 18 and 21 are rejected under 35 U.S.C. § 103(a), as allegedly being unpatentable over Anilionis et al. (WO 90/02557) in view of Nelson et al. (Infection and Immunity, 56(1):128-134, 1988) relied upon only for the description of P6, Guzman et al. (Journal of Bacteriology, 177(14):4121-4130, 1995) and Makrides et al. (Microbiology Reviews, 60(3):512-538, Sept. 1996). Applicants respectfully traverse this rejection.

According to the Office Action, "Anilionis et al specifically teach that bacterial host cell strains and expression vectors may be chosen which inhibit action of the promoter unless specifically induced (page 29, lines 27-30)… Anilionis et al does not teach that only their promoters would work[,] it directs the skilled artisan to others that would work and specifically direct to those that are inhibited unless specifically induced." Page 3. According to the Office Action, the tightly regulated pBAD promoter of Guzman meet the criteria of Anilionis for an inducible promoter.

In making the above rejection, the Office Action improperly merges two distinct aspects of promoter activity: specific induction and tight regulation. According to Anilionis, the lac promoter is a specific inducible promoter (page 29, lines 27-30). However, despite being a specific inducible promoter, the lac promoter is also a leaky promoter. *See* Green Declaration submitted on July 25, 2005 at Page 4 (the *lac*-promoted rP6 gene expresses easily detectable amounts of rP6 even in the absence of the IPTG inducer, which is another example of the leakiness of the *lac* promoter). Thus, contrary to assertions in the Office Action, Anilionis does not advocate the use of the tightly regulated promoter described in Guzman.

In fact, according to Anilionis, "it is desirable to use strong promoters in order to obtain a high level of transcription and, hence, expression of the gene." Conversely, according to Guzman, "maximum [expression] levels [obtained by their P_{BAD} vectors] are high enough to permit most studies that require

overproduction, they are not as high as those obtained from strong inducible promoters…" Page 4129, lines 38-43.

Accordingly, Anilionis advocates highly active expression systems with a strong inducible promoter, such as the leaky lac promoter, while Guzman uses tightly regulated promoters that "are not as high as those obtained from strong inducible promoters." *Compare* Guzman at page 4129, 2nd column, ("a great and often-overlooked disadvantage of many expression systems, including those repressed more efficiently, is that their promoters are too strong when they are induced and expression is not modulated… the resulting protein overproduction from these systems negates the physiological relevance of the experiments…") *with* Anilionis at page 29, 1st paragraph, ("it is desirable to use strong promoters in order to obtain a high level of transcription and, hence, expression of the gene.").

When combining references it is imperative that one step backward in time and into the shoes worn by the hypothetical "person of ordinary skill in the art" when the invention was unknown and just before it was made. In view of all factual information, the Examiner must then make a determination whether the claimed invention "as a whole" would have been obvious at that time to that person. MPEP § 2142.

Anilionis' criteria for a desirable expression vector is explicitly avoided in Guzman's vectors and Makrides and Nelson provide nothing further to support their combination. Accordingly, the references teach away, not toward the invention of the present claims.

"Under § 103, scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be

patented." KSR Intern. Co. v. Teleflex Inc., U.S. 2007 (2007 WL 1237837 (U.S.), at 6, citing *Graham v. John Deere Co. of Kansas City*, 86 S.Ct. 684. Notably, '[a] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *Id.* Unexpected results support a conclusion of non-obviousness. *Id.*

In addition to the foregoing, there are significant unexpected results and a long felt but unsolved need associated with the plasmids of the present claims. Numerous laboratories had tried for years to increase expression levels of lipidated P6 protein in *E. coli* and were unsuccessful. *See* Green et al., Infect. Immun. 58(10):3272-3278 and Yang et al, 1997, Vaccine 15:976-87, both cited in the May 29, 2003 IDS. It was only through discovery of the plasmids of the present claims that significant production of lipidated P6 protein was achieved in *E. coli*. *See* Green Declaration submitted on July 25, 2005 at paragraph 10. This result is entirely unexpected and solves a long felt need to provide immunogenic P6 proteins for vaccine compositions. *Id.*

The determination of obviousness is not the mechanistic overlaying of structural formulae to observe what structural overlaps exists. In re Ruschig, 52 C.C.P.A. 1238 (C.C.P.A., 1965). An unobvious property inherent in a claimed structure is sufficient to overcome a showing of structural similarity**,** and there is no basis in law for ignoring such property. *Id.*

The Office Action submitted on January 25, 2005 asserted that notwithstanding the significant unexpected results associated with the claimed plasmid, expression in lipidated form is a property of a vector in a specific host cell and not a structural property of the claimed plasmid. Page 8.

Plasmids are directed to more than just a particular structural formula. They inherently define properties associated with their expression. Accordingly, unobvious properties, such as the ability to express lipidated P6 protein in bacteria, are properties inherent to the plasmid and should not be dismissed.

Appellate courts are replete with cases dealing with compositions *per se* that were determined to be non-obvious in view of unexpected results associated

with the composition's intended use. *See* In re Mclamore 379 F.2d 985 (CCPA 1967) ("we consider the board's reasoning to be in error in that it refused to consider, as neither relevant nor controlling, the evidence of the results obtained and the arguments based thereon for the apparent reason that the claim is directed to the compound per se and not limited to any particular use. This we deem clearly in conflict with our decisions in *Ruschig,* in *Papesch,* and in the numerous precedents referred to therein. According to the principles we there expounded, in deciding the patentability of a compound all of its properties are to be taken into account.") or Takeda v. Alphapharm (Fed. Cir. 2007) at Page 20 (nontoxicity of compound ingested by mammals provides rebuttal of obviousness for claim to compound *per se*).

Guzman, Anilionis, Nelson and Makrides collectively fail to describe, and actually teach away from, the invention of the present claims. Furthermore the claimed invention provides significant unexpected results over the prior art. Accordingly, the rejection of claims 1, 2, 5, 8, 18 and 21 under 35 U.S.C. § 103(a) in view of Guzman, Anilionis, Nelson and Makrides is improper and should be withdrawn.

II. Claims 18 and 21 are rejected under 35 U.S.C. § 103(a), as allegedly being unpatentable over Anilionis et al. (WO 90/02557) in view of Nelson et al. (Infection and Immunity, 56(1):128-134, 1988) relied upon only for description of P6, Mertens et al. (Gene, 164:9-15, 1995) and Makrides et al. (Microbiology Reviews, 60(3):512-538, Sept. 1996). Applicants respectfully traverse this rejection.

According to the Office Action, the present claims do not exclude the presence of additional promoters other than T7 in the plasmid, therefore the promoter system of Mertens, which involves a dual λ_{PL} and P_{T7} promoter system is not excluded.

As amended, claim 18 teaches a plasmid containing a T7 promoter, wherein said T7 promoter is operatively linked to an isolated and purified DNA

sequence that encodes the P6 protein of *H. influenzae* (recombinant P6), wherein the recombinant P6 is under the control of only the T7 promoter.

Mertens describes "a versatile dual-promoter expression plasmid for heterologous gene expression in *Escherichia coli* which contains both λ_{PL} and P_{T7} promoters." Abstract. According to Mertens, "[g]enes placed under [only] T7 promoter control and which code for potentially toxic protein were difficult or impossible to maintain in such expression systems." Mertens et al., Biotechnology v. 13 (1995) pg 175-179 (at page 175, 2nd paragraph). Accordingly, Mertens in conjunction with Makrides teach away from the use of genes placed under the control of only the T7 promoter, as presently claimed. Accordingly, Applicants respectfully request withdrawal of the rejection.

III. Claim 20 is rejected under 35 U.S.C. § 103(a), as allegedly being unpatentable over Anilionis et al. (WO 90/02557) in view of Nelson et al. (Infection and Immunity, 56(1):128-134, 1988), Mertens et al. (Gene, 164:9-15, 1995) and Makrides et al. (Microbiology Reviews, 60(3):512-538, Sept. 1996), and further in view of Novagen Inc. allegedly admitted prior art (Specification page 15, line 34).

As described above, Anilionis, Nelson, Mertens and Makrides describe a different promoter system than what is being claimed. Novagen is relied upon solely for the description of a plasmid designated pPX4019. Accordingly, withdrawal of the rejection is respectfully requested.

CONCLUSION

Applicants would like to thank the Examiner for her thorough review of this application. In view of the amendments and remarks, it is submitted that the application is now in condition for allowance. Early notice to that effect is solicited. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned at (973) 660-6615.

Respectfully submitted,

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/Joel Silver/
Joel Silver
Reg. No. 53,866

Wyeth
Patent Law Department
Five Giralda Farms
Madison, NJ 07940
Tel. No. (973) 660-6615